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Renal perfusion and function in healthy African Americans

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Background. Despite their increased risk of nephropathy, remarkably little is known about renal perfusion and function in healthy African Americans.

Methods. We enrolled 32 healthy African Americans and compared renal perfusion and function in 82 age-matched healthy Caucasians. Studies were performed on a diet containing 200 mmol of sodium and 100 mmol of potassium per day. In a separate study of 28 subjects, 10 African American and 18 Caucasians, the contribution of the renin-angiotensin system was assessed by measuring renal hemodynamic responses to angiotension II (Ang II) and captopril.

Results. Although glomerular filtration rate (GFR) was similar, renal plasma flow (RPF) was significantly less in age-matched African Americans (568 ± 18) than Caucasians (620 ± 13 mL/min/1.73 m^2, $P = 0.0063$). After captopril, African Americans had a sevenfold greater vasodilator response and a rise in RPF (35.3 ± 4.9 vs. 4.9 ± 12.4 mL/min/1.73 m^2 in African Americans and Caucasians, respectively, $P < 0.028$). Ang II administration caused a significantly smaller vasoconstrictor response in African Americans (Ang II-induced fall in RPF, −97 ± 18 vs. −150 ± 9 mL/min/1.73 m^2, $P = 0.05$), and angiotensin-converting enzyme (ACE) inhibition enhanced the response to Ang II in African Americans significantly.

Conclusions. A reduction in RPF, blunting of the renal vascular response to Ang II, and an accentuated renal vasodilator response to captopril, which in turn corrects the blunting of responsiveness to Ang II, all suggest activation of the renin system in apparently healthy African Americans. As PRA was identical in Caucasians and African Americans, the findings suggest that it is the intrarenal-renin system that is activated in African Americans. This difference in normal control mechanisms could predispose to nephropathy.

African Americans shoulder a disproportionate rate of renal disease, mainly from hypertension and diabetes. In 1996, African Americans comprised 12.6% of the U.S. population, yet contributed 29.8% to end-stage renal disease (ESRD) [1]. Despite the striking increased risk of nephropathy, remarkably little information is available on renal function in healthy African Americans. In this study, we compared renal perfusion and function in healthy African Americans and Caucasians who were studied on a fixed sodium and potassium intake, as these are important determinants of renal perfusion.

We also took the opportunity to examine control mechanisms. Ethnicity is associated with variation in genetic polymorphisms [2, 3] and recently has been implicated in variation in renal perfusion and function in otherwise healthy individuals [4] The renin-angiotensin system (RAS) was selected because it makes such an important contribution to the control of renal perfusion in health and disease [6–8] and because of recent insights into possible genetic control mechanisms [9]. A common variant of the angiotensinogen (AGT) gene (methionine M235 replaced by threonine, T235) has been associated with altered renal control mechanisms in Caucasians [10], which is believed to reflect increased intrarenal formation of angiotensin II (Ang II). Blacks have a higher prevalence of this TT polymorphism [11]. We hypothesized that an activated intrarenal RAS could contribute to the propensity of African Americans developing ESRD, and used the response to an angiotensin-converting enzyme (ACE) inhibitor and to angiotensin II (Ang II) to test our hypothesis.

METHODS

Subjects

We studied 32 healthy African Americans (35 ± 2.7 years) and 82 healthy age-matched Caucasians (38.0 ± 1.8 years) in balance on a high-salt diet. All were free of cardiovascular, renal, and endocrine disease. After an outpatient evaluation, which included a history, physical examination, and appropriate laboratory studies, eligible subjects were admitted to the protocol. The majority of the subjects used no medication other than vitamin supplements. There were three patients who used ventalin and beclovent inhalers. All subjects were studied

Key words: ethnicity and kidney function, ACE inhibition, angiotensin II, race and kidney, hypertension, diabetes, renin system.

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during admission to a metabolic ward, the General Clinical Research Center of Brigham and Women's Hospital. Written informed consent was obtained from each subject, and the protocol was approved by the Human Subjects IRB Committee.

Three days before admission, subjects were placed on a high-salt diet (200 mmol sodium per day) and daily 24-hour urine collections taken for measurement of sodium, potassium, protein, and creatinine excretion. Each subject was admitted 24 to 48 hours prior to the study day and was maintained on a 200 mmol sodium and 100 mmol potassium constant isocaloric diet, with at least 2500 mL of fluid intake. Subjects were studied when 24-hour urine sodium was greater than 150 mmol.

Protocol sequence

Subjects fasted overnight and remained recumbent throughout the study. One intravenous catheter was placed in each arm at least two hours before the study, one for infusions and the other for blood drawing. Para-aminohippurate (PAH) and inulin were infused, and clearances reflected renal plasma flow (RPF) and glomerular filtration rate (GFR), respectively, as described previously [8]. Studies began at approximately 7 a.m. with a bolus and then continuous infusion of PAH and inulin. Baseline PAH and inulin measurements were made 60 minutes later.

A different group of 28 subjects, 10 healthy African Americans (age 28 ± 2 years) and 18 Caucasians (age 30 ± 2 years), participated in a more extensive protocol. After baseline renal clearance measurements were made, Ang II (Hypertensin, Ciba) was infused for 45 minutes at 3 ng/kg/min. This dose was used because it has been found to influence RPF with minimal pressor effects. Immediately following, each subject received a single oral 25 mg dose of captopril, known to be at the top of the renal vasodilator dose–response curve [12]. To assess the effect of captopril on the tissue sensitivity to Ang II, the Ang II infusion was repeated 90 minutes after captopril was given. RPF and GFR measurements were made at baseline and at 45-minute intervals. Plasma renin activity (PRA) and aldosterone were measured at baseline and at 90 minutes. Blood pressure was recorded by an automatic recording device (Dinamap, Critikon) at 15-minute intervals and at 2-minute intervals during the Ang II infusion.

Laboratory procedures

Blood samples were collected on ice and spun immediately, and the plasma was stored at −80°C until the time of assay. Serum and urinary sodium and potassium levels were measured using the ion-selective electrode. Serum creatinine, PAH, and inulin were measured by an autoanalyzer technique [7]. PRA and aldosterone were measured by radioimmunoassay [13].

Table 1. Baseline characteristics of the 114 healthy subjects

	African Americans	Caucasians
N	32	82
Age *years*	35 ± 3.0	38 ± 1.8
MAP *mm Hg*	89 ± 1.7	86 ± 1.0
BMI kg/m^2	26.4 ± 0.8[b]	23.9 ± 0.4
Weight *kg*	79.8 ± 3.4[b]	72.3 ± 1.2
K^+ *mEq/L*	4.1 ± 0.1	4.1 ± 0.1
PRA *ng/mL/hr*	0.5 ± 0.1	0.6 ± 0.1
Aldosterone *ng/dL*	5.4 ± 1.0	4.7 ± 0.3
Urine Na^+ *mEq/24 hr*	223 ± 13.7	217 ± 8.9
Urine K^+ *mEq/24 hr*	50 ± 3.8[c]	78 ± 2.3
RPF $mL/min/1.73\ m^2$	568 ± 18.2[b]	620 ± 12.8
GFR $mL/min/1.73\ m^2$	115 ± 2.9	111 ± 1.8
Filtration fraction %	20 ± 0.5[a]	19 ± 0.4

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.0001$

Statistical analysis

The primary endpoint studied was the magnitude of change in RPF in response to captopril and exogenous Ang II. All data are expressed as mean ± SEM. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Mean arterial pressure (MAP) was calculated as diastolic pressure + (systolic − diastolic)/3. Statistical differences in two sample data were assessed by *t*-test or nonparametric (Wilcoxon rank sum test). The null hypothesis was rejected when the *P* value was less than 0.05.

RESULTS

The 32 African Americans and 82 Caucasians in this study were all matched for age, mean arterial blood pressure, serum electrolytes, and sodium balance, as reflected in 24-hour sodium excretion (Table 1). Plasma renin activity and plasma aldosterone concentration were not statistically different in African Americans and Caucasians. The African Americans, on the other hand, were significantly heavier.

Baseline RPF was significantly lower in African Americans (568 ± 18 vs. 620 ± 13 mL/min/1.73 m^2, $P < 0.03$; Table 1). As age is a major determinant of renal perfusion, the relationship between age and RPF in blacks and whites was examined (Fig. 1). The anticipated highly significant negative relationship between age and RPF in the 82 Caucasians was identified. Age accounted for approximately one third of the variation in RPF over an age range of 18 to 79 years in the Caucasians ($r = 0.58$, $r^2 = 0.336$, $P < 0.001$). RPF also fell with age in the African Americans ($r = 0.375$, $r^2 = 0.141$, $P = 0.035$; Fig. 1B). The dashed line in Figure 1B represents the line of the best fit for the Caucasians. In the blacks, 24 of 32, or 75%, of the points fell below the line for the Caucasians. Graphically, the age-related difference disappeared at approximately age 70 years.

Baseline characteristics for the 28 subjects who partici-

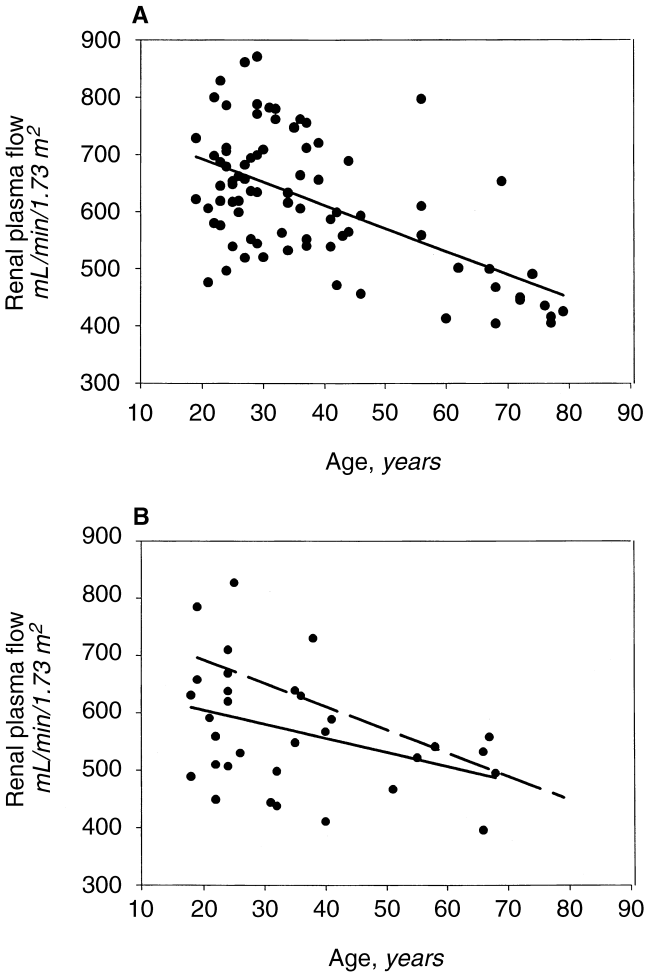

Fig. 1. (*A*) Relationship between age and renal plasma flow (RPF) measured as para-aminohippurate (PAH) clearance in 82 Caucasians. The anticipated highly significant negative relationship was found (y = 774–4.1 x; r = 0.58, f = 41.1, N = 82; $P < 0.001$). The dashed line represents the line of best fit in the Caucasians. (*B*) Relationship between age and para-aminohippurate (PAH) clearance in healthy African Americans. The solid line represents the line of best fit in the blacks. Three quarters of the points in the blacks fall below the line of best fit in Caucasians (y = 654–2.46 x; r = 0.38, f = 4.9, N = 32; $P < 0.035$). The age-related difference disappears at approximately age 70.

Table 2. Baseline characteristics of the 28 healthy subjects

	African Americans	Caucasians
N	10	18
Age *years*	27.5 ± 2.4	29.6 ± 1.9
MAP *mm Hg*	88 ± 4.8	82 ± 1.7
BMI *kg/m²*	28.2 ± 1.4[a]	23.4 ± 0.7
Weight *kg*	85.5 ± 5.1[c]	68.7 ± 2.5
K^+ *mEq/L*	4.1 ± 0.1	4.2 ± 0.008
PRA *ng/mL/hr*	0.36 ± 0.05	0.37 ± 0.008
Aldosterone *ng/dL*	3.7 ± 0.4	3.5 ± 0.3
Urine Na^+ *mEq/24 hr*	213 ± 20	258 ± 22
Urine K^+ *mEq/24 hr*	36.4 ± 3.7[d]	59.8 ± 6.1
RPF *mL/min/1.73 m²*	517 ± 27[b]	600 ± 14
GFR *mL/min/1.73 m²*	110 ± 4	118 ± 6
Filtration fraction %	21.5 ± 0.7	20.3 ± 0.01

[a] P = 0.002 blacks vs. whites
[b] P = 0.0006 blacks vs. whites
[c] P = 0.003 blacks vs. whites
[d] P = 0.01 blacks vs. whites

Table 3. Renal hemodynamic response to captopril

	African Americans		Caucasians	
	Before ACEI	After ACEI	Before ACEI	After ACEI
RPF *mL/min/1.73 m²*	517 ± 27	555 ± 27	600 ± 14	605 ± 16
GFR *mL/min/1.73 m²*	110 ± 4	110 ± 4	118 ± 6	111 ± 4
Filtration fraction %	22 ± 0.7	20 ± 0.6	20 ± 0.01	20 ± 0.008

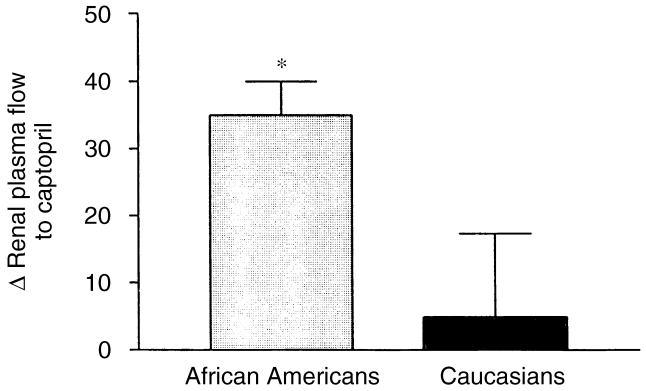

Fig. 2. Renal vascular response to angiotensin-converting enzyme (ACE) inhibition with captopril in healthy African Americans (□) and whites (■; $P < 0.028$ blacks vs. whites).

pated in the detailed substudy are presented in Table 2. Again, the African Americans and Caucasians were not statistically different with regards to age, MAP, plasma K^+, sodium excretion, PRA, aldosterone level, and GFR. BMI and body weight again were higher in the African Americans. Although baseline GFRs were comparable, RPF was again significantly lower in the African Americans compared with Caucasians (517 ± 27 vs. 600 ± 14 mL/min/1.73 m², P = 0.006).

After receiving captopril, the African Americans had a significant rise in RPF (517 ± 27 to 555 ± 27 mL/min/1.73 m², $P < 0.0001$), while RPF in the Caucasians was unchanged (600 ± 14 to 605 ± 16 mL/min/1.73 m²; Table 3). The change in RPF from baseline was significantly different in the two groups (35.0 ± 5 vs. 4.9 ± 12.4 mL/min/1.73 m², $P < 0.028$ for African Americans and Caucasians, respectively; Fig. 2). With the significant vasodilator response after captopril administration in the blacks, RPF in the two groups became more similar (555 ± 27 vs. 605 ± 16 mL/min/1.73 m²). GFR did not change in either group in response to captopril. Although filtration fraction trended downward in the African Americans after captopril, the fall did not reach significance (Table 3). Ang II administration (Table 4) caused a sig-

Table 4. Renal responses to Ang II before and after captopril

	African Americans		Caucasians	
	Before ACEI	After ACEI	Before ACEI	After ACEI
ΔRPF to Ang II *mL/min/1.73 m²*	−97.3 ± 17.6[a]	−116.8 ± 18.5[b]	−150.1 ± 9.4	−128.7 ± 14

[a] $P = 0.007$ ΔRPF to Ang II from baseline in African Americans vs. Caucasians before captopril
[b] $P = 0.049$ ΔRPF to Ang II from baseline in African Americans before vs. after administration of captopril

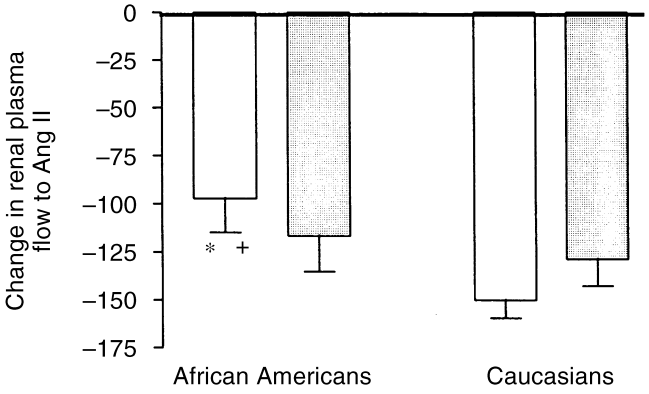

Fig. 3. Renal vascular response to Ang II in African Americans and Caucasians before (□) and after (■) captopril. Note that the Caucasians had no significant difference in response with or without captopril. The African Americans after captopril responded similarly to Ang II as the Caucasians. *$P < 0.007$ ΔRPF to Ang II from baseline in African Americans vs. Caucasians before captopril; +$P < 0.049$ ΔRPF to Ang II from baseline in African Americans before vs. after administration of captopril.

nificantly blunted vasoconstrictor response in the African Americans compared with the Caucasians (ΔRPF −97 ± 18 vs. −150 ± 9 mL/min/1.73 m², African Americans vs. Caucasians, respectively, $P = 0.007$). After the administration of captopril, the vasoconstrictor response to exogenously administered Ang II was enhanced significantly in the African Americans (−97 ± 18 to 117 ± 19 mL/min/1.73 m², $P = 0.0488$; Fig. 3), whereas the response was unchanged in the Caucasians. The subjects were all normotensive. Mean arterial pressure (MAP) was 88 ± 5 and 82 ± 2 mm Hg in the African Americans and Caucasians, respectively (Table 2). Blood pressure in response to captopril did not change significantly in either African Americans (88 ± 5 to 83 ± 7 mm Hg) or Caucasians (82 ± 2 to 82 ± 2 mm Hg). The 24-hour urine collections, done to verify sodium balance, were also collected for protein measurements. All of the subjects had protein excretion of less than assay range (<60 mg/dL).

DISCUSSION

Although the prevalence of renal disease is increased in African Americans, we can find no report on renal hemodynamics in healthy blacks. The few renal hemodynamic studies that have been performed in African Americans involve diseased kidneys [14, 15] This study was designed to assess two linked hypotheses. Our first hypothesis was that RPF would be reduced in apparently perfectly healthy blacks. Our second hypothesis was that this difference would reflect activation of the intrarenal RAS. The data strongly support both hypotheses. RPF was about 10% lower in healthy age-matched African Americans than in Caucasian participants. Despite a similar PRA in the African Americans, there was a significant enhancement of the renal vasodilator response to ACE inhibition with captopril in the African Americans, even on the high-salt diet employed to suppress the circulating RAS.

The mechanism of this renal vasodilator response to captopril appears to have involved a reduction in Ang II formation, rather than a reduction in bradykinin degradation, and thus prostaglandin and nitric oxide formation. This conclusion is based on the pattern of responses to Ang II. Prior to captopril administration, the renal vascular response to Ang II was blunted in African Americans. We used as probes the RPF response to exogenously administered Ang II and blockade of the RAS with captopril in high-salt balance. The limited response seen in the African Americans is similar to what we have experienced in healthy Caucasians in a low-salt state [17] when the RAS is activated. When given captopril at the top of its dose response for the kidney [12], African Americans experienced sevenfold more vasodilation. As in previous studies incorporating a high-salt diet, Caucasians vasodilated little when given captopril [16] probably because their intrarenal RAS is more suppressed. In accord, Ang II administration in the presence of captopril showed an enhanced response in African Americans. This response probably reflects increased local Ang II in the kidney. If the vasodilator response to captopril had involved kinins or the other vasodilator pathways, the consequence would have been a further blunting of the renal vascular response to Ang II [18]. The potentiation of the renal vasoconstrictor response to Ang II after captopril, in this context, provides strong evidence that a reduction in Ang II formation was the dominant mechanism responsible for the renal vasodilator response to captopril in healthy African Americans. A difference in salt intake is unlikely to account for these differences in the control of the renal

circulation by ethnicity, as all studies were performed on a metabolic ward and on a controlled diet, and 24-hour urine collections revealed an excretion rate that was essentially identical in the two groups. The sodium in the diet is similar to the average sodium intake in the community.

Hopkins et al reported that an AGT polymorphism in which threonine replaces methionine at codon 235 is associated with a blunted RPF response to infused Ang II in Caucasians and suggested that this may represent increased intrarenal Ang II [10]. The frequency of this polymorphism is much higher in blacks [11] than Caucasians. We hypothesized that African Americans therefore might have activation of the intrarenal RAS on the same genetically determined basis. This, in turn, could be an underlying mechanism contributing to race-related differences in renal disease. African American's familial clustering of ESRD is more striking than in Caucasian families [24, 25]. Polymorphisms of the *AGT* gene might be involved, as this polymorphism is associated with a renal state resembling our findings in blacks, and this polymorphism is found at higher frequency in blacks [11]. In blacks, obesity and consequent elevated insulin levels may also play a role in increasing AGT. We will need studies in substantially more than 32 African Americans before assessment of the relationship of phenotype to genotype is possible.

Body mass index was higher in the African Americans (Tables 1 and 2). Many studies have reported increased body weight in African Americans [18]. African Americans in our study showed lower basal RPFs compared with Caucasians. Chagnac et al found in normal, healthy, severely obese individuals (BMIs of 43.8 ± 1.0) that the RPF exceeded the controls by 31% [34]. Race was not characterized. We found no correlation, however, between body weight and response to captopril or Ang II. It is becoming widely recognized that obesity plays some role in the pathogenesis of hypertension and type 2 diabetes mellitus, and there may be a link between obesity and altered renal function [10]. Obesity was found to be a strong predictor of blunted renal responses to Ang II [10].

Renal mass varies with body size in adults [19]. Therefore, the need to normalize for body size has been intuited. The standard practice has been to use a body surface area of 1.73 m^2 [10, 20]. Depending on whether normalization for body surface area was used, renal perfusion could be less than anticipated or exceed expectation in the obese. To address this issue, Porter used radioactive xenon to measure RBF in a group of lean and obese healthy kidney donors [21]. Because blood flow as registered as mL/100 g/min with this method, no further adjustment for kidney or body size was necessary. As the obese subjects did not have a lower RPF, the normalization procedure, which results in a reduction in apparent RPF, does not reflect intrarenal events. Although the African Americans in this study were not morbidly obese, their BMI was significantly higher than Caucasians ($P = 0.04$ in the group of 114 and 0.0002 in the smaller cohort). To assess the issue of normalization to body surface area, we also examined non-normalized values for RPF in mL/min. The vasodilator response to captopril was still apparent (40 ± 6 vs. 5 ± 13 mL/min for African Americans vs. Caucasians, $P = 0.015$). Although the normalization did not appear to play a role in our findings, more work is needed to investigate mechanisms of obesity-related renal responses.

Plasma renin levels were not statistically different in the two groups, and not lower in the healthy African Americans, as had been reported [22, 23]. As is the case for the renal blood supply, we know a great deal about the state of the RAS in African Americans with hypertension and renal disease and remarkably little about the state and responsiveness of this system in healthy blacks.

What mechanisms could be involved in the lower basal RPF in healthy African Americans? We hypothesized a genetic factor, and that remains a possibility; however, our research also uncovered a possible environmental contributing factor: potassium. A reduction in potassium intake has been described repeatedly in African Americans [29]. We have shown an influence of dietary potassium intake on the RAS, renal perfusion, and its response to Ang II that is relevant to this study. In healthy Caucasians, a reduced potassium intake was associated with a significant increase in circulating renin activity, a significant reduction in renal blood flow, and a decrease in the renal vascular response to infused Ang II, as we found in blacks in this study. The potassium intake necessary to induce these measurable responses was very low, approximately 40 mmol/day [33]. Although potassium intake was controlled at the same high level in both Caucasians and blacks in our study, this control period lasted only one to two days, perhaps not long enough to replete a deficiency. Serum potassium was identical in the two groups, but 24-hour urine potassium excretion was significantly lower in African Americans. Clearly, experiments in which a high potassium intake is maintained for a longer interval will be important.

Other hormones that can influence renal hemodynamics are also possible contributors. The kallikrein-kinin system has a vasodilator effect on the kidney. There is evidence that renal kallikrein-kinins play a role in blood pressure regulation and in the pathogenesis of hypertension [26, 27]. Urinary kallikrein excretion has been found to be decreased in hypertensives [28] and African Americans [29, 30]. Some polymorphisms of the kallikrein gene have been identified predominantly in African Americans [31]. Recently, genetic variability in one of the isoforms involved in the synthesis of nitric oxide has been

linked to advanced nephropathy in type 1 diabetes mellitus [32]. Whether there is an increased prevalence of this polymorphism in blacks is unknown. More work is clearly required in the study of candidate genes related to renal disease.

Ethnicity as a contributor to differences in the frequency of ESRD is widely recognized. Despite that recognition, there has been remarkably little investigation into the environmental and genetic factors that might contribute to such a difference. In Kuna Amerinds, for example, a pattern of renal perfusion and GFR that differs striking from that in Caucasians has been described [4]. This study extends investigation into the possibility that ethnicity contributes to differences in renal perfusion and function in healthy blacks and whites. Environmental factors such as short-term sodium, potassium, and protein intake, body position, and time of day are controlled easily on a metabolic ward and clearly contributed little or nothing to the difference in this study. More long-term environmental factors involving diet or socioeconomic factors might participate through mechanisms that are currently not recognized.

The triad of blunted vasoconstriction in response to Ang II, marked renal vasodilation with an ACE inhibitor, and enhancement of vasoconstriction to Ang II after captopril—in the presence of a PRA level that is identical to that in Caucasians—suggests increased levels of Ang II in the kidneys of these individuals. African Americans, with a lower RPF and an activated intrarenal RAS, might thereby be at greater risk of ESRD than age-matched Caucasians. The susceptibility to renal injury would be expressed when triggers such as hypertension, diabetes, or HIV infection are superimposed.

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